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ORIGINAL STUDY

Metal ion levels decrease after revision for metallosis arising from large-diameter metal-on-metal hip arthroplasty

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Concerns have been renewed regarding the possible long-term effects of elevated circulating levels of cobalt and chromium as a direct result of implantation of large femoral head diameter metal-on-metal bearings.

In order to establish whether metal ion levels remain persistently elevated, we compared metal ion levels before and after revision surgery in patients with large head diameter (greater than 38 mm) metal-on-metal total hip arthroplasty or hip resurfacing arthroplasty.

At greater than one year post removal of a large-diameter metal-on-metal hip implant for the indication of symptomatic metallosis, metal ion levels were found to fall to almost normal levels.

Keywords : metal-on-metal ; revision total hip arthroplasty ; metal ion levels.

INTRODUCTION

Total hip arthroplasty and hip resurfacing are successful and established procedures offering pain relief and improving quality of life. Over time, surgery has been undertaken to younger, more active cohorts of patients wishing to preserve a higher level of activity and range of motion. Large femoral heads confer implant stability by increasing head-neck ratio and hence range of motion before component-component impingement and jump distance to subluxation (*4,13*).

Large-diameter femoral heads in metal on polyethylene pairing generate more debris and wear particles responsible for periprosthetic osteolysis and aseptic loosening (*19,26*). Advances in implant technology and engineering have created metal-on-metal (MoM) articulations which offer extremely low rates of wear (*1*) and permit use of large head sizes which yield between 20-100 times less debris than their metal-on-polyethylene counterparts (*23*). However, although metallic wear particles are in the nanometer size range and hence volumetrically

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smaller than their polyethylene counterparts, they are more numerous and are biologically active, giving rise to elevated levels of Cobalt (Co) and Chromium (Cr) ions found in serum and urine as wear particles corrode and dissolve (*3,7,21,22*).

High levels of Co and Cr ions may give rise to local and systemic toxic effects. Local effects include metallosis described as the infiltration of metallic wear debris into periprosthetic structures, which has been suspected to give rise to soft tissue toxicity and implant failure via a delayed type IV hypersensitivity reaction described as an aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) (*25*). High levels of metal bearing wear particles have also been implicated in the formation of localised pseudotumours (*20*). Early concerns over the possibility of elevated Co and Cr levels having mutagenic or carcinogenic properties have not yet been conclusively proven (*2,16*).

No reports in the literature exist as to whether circulating levels of Chromium (Cr) and Cobalt (Co) decrease upon removal of a symptomatic large-diameter MoM implant or whether levels remain high due to the effect of metal debris embedded in the soft tissues after revision surgery.

PATIENTS AND METHODS

Between June 2006 and June 2009 we undertook 44 revision surgeries of both large-head MoM THAs (femoral head diameter ≥ 38 mm) and metal-on-metal hip resurfacings, for suspected metallosis. Patients underwent revision surgery at a single institution. Both femoral and acetabular components were revised to either a metal on polyethylene or ceramic on ceramic bearing. Mean time from original implant to revision was 4 years, 8 months (range : 1 yr 4 mo-7 yr 9 mo). These patients were enrolled in a prospective, independent study. Informed consent was taken from patients at the time of their operation with all patients agreeing to long term clinical and radiological follow-up.

All hip arthroplasties were prospectively registered on a computerised database. We contacted patients who had undergone revision surgery for suspected metallosis arising from a large-head MoM THA or resurfacing arthroplasty at least one year earlier and asked them to attend a dedicated clinic. Patients completed an Oxford Hip Score and provided a sample of blood for analysis of Co and Cr.

The primary outcome measure was venous whole blood Cr and serum Co in nM/L at greater than one year following revision surgery. Whole blood analysis of Cr has been found to provide a better estimation of systemic metal ion exposure than analysis of plasma or serum alone (*9*). This is due to wide variation in Cr levels in plasma compared to those in serum and as Cr can tend to accumulate in red blood cells, neither plasma nor serum levels accurately reflect total blood exposure. Co was measured as serum Co following the recommendations outlined by MacDonald *et al* (*15*). Blood samples were obtained using a 21-gauge stainless steel needle (BD304432 BD Microlance™ , Becton Dickinson). The first 10ml of blood was discarded to avoid contamination. Samples were collected in two 4ml EDTA tubes (Sarstedt Monovette, Numbrecht, Germany). Blood samples were submitted for analysis to the Supraregional Assay Service, Trace Elements Section, Toxicology laboratory, City Hospital, Birmingham UK. Levels of Co and Cr were determined by Inductively Coupled Plasma Mass Spectrometry (Agilent 7500CX).

Comparison was made with reference levels indicated by the Medicines and Healthcare Regulatory Agency recommendation of less than 7ppb for Cr (130 nM/L) and Co (120 nM/L) (*17*).

Statistical analysis was undertaken using Sigmaplot software (Systat Software Inc, Chicago, IL). Differences in metal ion levels before and after revision surgery were analyzed for significance using the Mann-Whitney Rank Sum test. A 95% ($P < 0.05$) confidence interval was applied for statistical significance.

RESULTS

Forty two patients (M:F = 19:23, median age 61 years) were found to have histological evidence of either metal allergy, metal toxicity or foreign body reaction. Two patients had evidence of infection with no features of metal reaction. One patient had infective complications necessitating Girdlestones. Three patients suffered early dislocation requiring closed reduction.

The mean follow-up evaluation was at 2 years and 2 months (range : 1 yr 2 mo-4 years). Eleven patients were lost to follow-up. Eight patients were diagnosed pre operatively on Co and Cr levels in urine or synovial fluid aspirate alone. Of the patients revised for metal hypersensitivity or metallosis and who attended follow-up (n = 31), mean

post revision levels were as follows : Co = 91.1 nM/L (range = 19-885 nM/L) and Cr = 57.47 nM/L (range = 1.7-1575.9 nM/L). Only one patient had persistently elevated levels of Co and Cr due to having a contralateral symptomatic MoM articulation *in situ* which was awaiting revision at time of follow-up.

Twenty three patients had pre revision blood or serum metal ion level results available for direct comparison (M:F = 10:13). There was no statistically significant difference in metal ion levels between males and females pre and post revision. Of these 23 patients, 19 patients had undergone primary THR using a large-head MoM implant (4 ASR, 9 Birmingham Freeman Hybrid, 2 Corail Pinnacle, 1 other) with the remaining 4 patients having a Birmingham Hip Resurfacing Arthroplasty.

There was no significant difference in whole blood Cr levels between MoM THR and MoM hip resurfacing arthroplasty. The pre-revision median serum levels of Co were significantly higher ($p < 0.01$*) for MoM THRs (178.5 nM/L) than MoM hip resurfacing arthroplasty (51 nM/L). Post revision median serum levels of Co were significantly lower ($p < 0.01$*) for MoM THRs (5.1 nM/L) versus MoM hip resurfacing arthroplasty (28.8 nM/L).

The pre- and post revision serum Co and whole blood Cr levels respectively are summarized in Fig. 1 & Table 1. Median serum Co level pre revision was 176.6 nM/L, falling significantly post revision to 5.1 nM/L ($p = < 0.001$*). The median whole blood Cr level pre revision was 117 nM/L and fell significantly to 19 nm/L post revision ($p = < 0.001$*). Following revision surgery, mean Oxford Hip Score was 23.7.

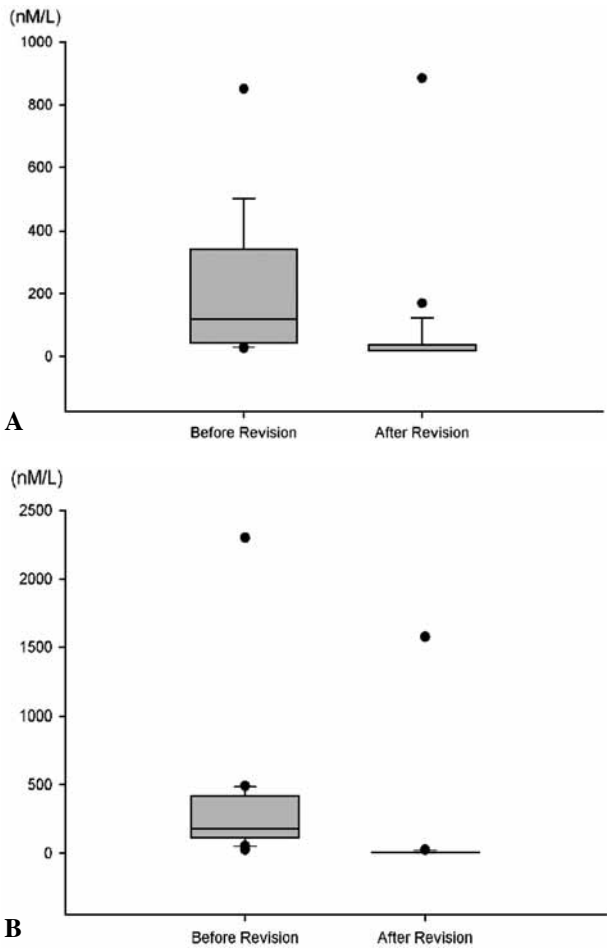

Fig. 1. — Whole blood concentration of Chromium (A) and serum Cobalt (B) before and after revision surgery.

DISCUSSION

Despite initial promise of decreased wear rates and increasing suitability for use in younger more active patients, concerns remain about potential adverse consequences of MoM bearing surfaces in terms of aseptic loosening and pain secondary to soft tissue reaction to metal debris.

Elevated circulating levels of metal ions following MoM THR or resurfacing arthroplasty are not uncommon (*3,8,24*) with metal ion levels reaching a steady state approximately one year following first implantation (*10*). The biological pathways leading to adverse periprosthetic soft tissue reactions associated with metal debris have yet to be conclusively demonstrated, but may represent a delayed type IV (ALVAL) hypersensitivity reaction with subsequent effect on local cell populations in susceptible individuals, giving rise to painful soft tissue mass or pseudotumour as well as osteolysis and loosening (*14*). However, it has been suggested that these soft tissue reactions may be the result of increased wear that is directly correlated with elevation of metal ions *in vivo* where the presence of extensive necrosis and macrophage infiltrate implies a metal debris cytotoxicity (*11*).

Table I. — Comparison of metal ion values before and after revision surgery for suspected metallosis

Ion (nM/L) (n = 23)	Before revision	After revision	P value*
Serum cobalt			
Mean ± SEM (median)	307.1 ± 99.72 (176.6)	6.56 ± 1.13 (5.1)	< 0.001*
Range	25-2300	1.7-23.8	
Whole blood chromium			
Mean ± SEM (median)	204.54 ± 44.60 (117)	67.34 ± 37.75 (19)	< 0.001*
Range	25-850	19-885	

Our study demonstrates that at greater than one year following revision surgery for clinically suspected metallosis in patients with large-diameter MoM hip resurfacings and arthroplasties, Co and Cr levels return to almost normal levels. Given our small cohort size it is not possible to draw conclusions as to differences in metal ion release for individual implant types, but there appeared to be no significant difference in pre or post revision whole blood Cr levels between large-diameter MoM THRs and MoM hip resurfacing arthroplasty. Due to our small sample size it is not possible to comment as to why serum Co levels fall more significantly in MoM THRs than for hip resurfacings.

Metal ion release appears to be positively correlated with increasing bearing diameter, with one series suggesting that this is particularly true for large-diameter MoM THAs since open femoral head design confers greater contact surface for passive metal corrosion and ion release from components with Co-Cr modular junctions and double tapers (*12*).

Our main limitation was that the number of patients whose pre and post revision blood and serum metal ion levels we had for direct comparison was compromised by inconsistency of objective measurements in diagnosis. Many patients presenting in the early stages of the study had a diagnosis made on the basis of clinical and radiological suspicion, elevated metal ions in urine, joint aspirate, blood samples in any combination.

Previously there has been no clear consensus as to how to evaluate patients with suspected metallosis arising from MoM articulations which makes retrospective analysis difficult due to a variety of different assays used and inconsistent histological nomenclature (*5*). There appears to be no coherence in the literature to define the boundaries of the terms metallosis, ALVAL, and pseudotumour to distinguish if these are distinct separate entities or if they represent a spectrum under the umbrella term of adverse reactions to metal debris (ARMD) proposed by Langton *et al* (*12*). Additionally the prognostic significance of the degree of soft tissue staining by metal debris observed intraoperatively has yet to be proven (*6*).

In the UK the Medical and Healthcare Products Regulatory Agency has issued Medical Device Alerts on the basis of a minority of patients with metal-on-metal articulations developing progressive soft tissue reactions secondary to metal wear debris. It is proposed that patients with MoM articulations be followed up annually for the first five years and that patients presenting with abnormally painful MoM hip replacements, should be evaluated for blood Co and Cr as well as cross sectional imaging if patients have metal ion levels above 7 ppb, radiological features associated with adverse outcome, have small component size hip resurfacing arthroplasty or where patient or surgeon is concerned about the MoM articulation. The recommendation is to consider early revision if metal ion levels are found to be elevated upon repeating at three months and/or if imaging reveals soft tissue reactions, fluid collections or tissue mass (*15*). The recent recall of DePuy ASR systems due to a higher than expected revision rate has extended the scope of these initial recommendations to include

those patients with ASR hip implants *in situ* who present with limping, swelling around the hip, and deteriorating hip function (*18*).

Given the widespread use of large-diameter MoM implants, larger cohort studies are needed to assess the actual incidence of metallosis with respect to the varying implant designs. Despite our initial finding that metal ion levels significantly return to near normal levels at one year following revision surgery, future follow-up studies will be required to establish the longer term consequences of metallosis.

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